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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/477,082	12/30/1999	VINCENT J. KIDD	2427/IE988-U	8684
29311	7590	06/04/2002	EXAMINER	
DARBY & DARBY 805 THIRD AVENUE NEW YORK, NY 10022-7513			HUNT, JENNIFER ELIZABETH	
ART UNIT		PAPER NUMBER		
1642		DATE MAILED: 06/04/2002		16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/477,082	Applicant(s) Kidd et al.
	Examiner Jennifer Hunt	Art Unit 1642
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>		
Period for Reply		
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.		
<ul style="list-style-type: none"> - Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b). 		
Status		
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Feb 19, 2002</u>		
2a) <input checked="" type="checkbox"/> This action is FINAL . 2b) <input type="checkbox"/> This action is non-final.		
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11; 453 O.G. 213.		
Disposition of Claims		
4) <input checked="" type="checkbox"/> Claim(s) <u>2-9, 11-25, and 27-57</u> is/are pending in the application.		
4a) Of the above, claim(s) <u>21-25 and 30-47</u> is/are withdrawn from consideration.		
5) <input type="checkbox"/> Claim(s) _____ is/are allowed.		
6) <input checked="" type="checkbox"/> Claim(s) <u>2-9, 11-20, 27-29, and 48-57</u> is/are rejected.		
7) <input type="checkbox"/> Claim(s) _____ is/are objected to.		
8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.		
Application Papers		
9) <input type="checkbox"/> The specification is objected to by the Examiner.		
10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).		
11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.		
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.		
Priority under 35 U.S.C. §§ 119 and 120		
13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).		
a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of: 1. <input type="checkbox"/> Certified copies of the priority documents have been received. 2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____. 3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).		
*See the attached detailed Office action for a list of the certified copies not received.		
14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).		
a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.		
15) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.		
Attachment(s)		
1) <input type="checkbox"/> Notice of References Cited (PTO-892)		
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____		
4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____		
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)		
6) <input type="checkbox"/> Other: _____		

Art Unit: 1642

Response to Amendment

1. Acknowledgment is made of applicant's cancellation of claims 1, 10, and 26, and addition of new claims 48-57. Claims 2-9, 11-25, and 27-57 are pending in the application. Claims 21-25 and 30-47 have been withdrawn from consideration as being drawn to a non-elected invention.
2. This application contains claims 21-25 and 30-47, drawn to an invention nonelected with traverse in Paper No. 12. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
3. Claims 2-9, 11-20, 27-29, and 48-57 are considered herein.
4. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Claim Rejections Withdrawn

5. The rejections of claims 1, 10, and 26 are withdrawn in light of the cancellation thereof.
6. The rejection of pending claims 6-8, and 17-19 under 35 U.S.C. 102(b) as being anticipated by Mandruzzato et al., J. Exp. Med., Vol. 186, No. 5, pages 785-793, August 29, 1997, (IDS) is withdrawn in light of the amendments thereto.

Art Unit: 1642

7. The rejection of pending claims 4-6, and 15-17 under 35 U.S.C. 103(a) as being unpatentable over Mandruzzato et al., J. Exp. Med., Vol. 186, No. 5, pages 785-793, August 29, 1997, (IDS), in view of Herman et al. (1), PNAS, Vol. 93, pages 9821-9826, September 1996, or Herman et al. (2), PNAS, Vol. 91, pages 9700-9704, October 1994 is withdrawn in light of the amendments thereto.

Claim Rejections Maintained/New Grounds of Rejection

8. The previous grounds of rejection under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the recitation of "poor prognosis" is applied to newly added/amended claims 11-20, and 51-54.

As set forth in the previous office action, the term "poor prognosis" is a relative term which renders the claim indefinite. The term "poor prognosis" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of a "poor prognosis" cannot be determined, and thus it is not clear what would be considered a "poor prognosis" and what would not.

Applicant argues that the term "poor prognosis" is well known in the art to mean "less likely than others to get well", and further that the specification defines the term as "poor

Art Unit: 1642

prognosis for outcome of treatment of the cancer, at least by conventional therapies”, and that amended claims recite this exact recitation from the specification. Applicant's arguments filed February 19, 2002 have been fully considered but they are not persuasive.

As set forth in the previous office action the term “poor prognosis” does not provide a standard for determining the scope of the invention. The definition argued by applicant as art standard (less likely than others to get well) does not further clarify the metes and bounds of this relative term. Specifically, it is not clear how to measure or determine the likelihood of one patient to get well, versus the likelihood of any other patient to get well.. Further, what would be considered “getting well”? How great must a recovery be, and for how long must it last to be considered “getting well”? Further, the recitation from the specification provides no more guidance as to the standards for determining a “poor prognosis”. Thus the recitation in the claims and the guidance in the specification fail to establish what characteristics a disease process must embody to have a “poor prognosis.”

9. Claims 2-9, 11-20, 27-29, and 48-57 are newly rejected under 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the newly added recitation of “reduction in the total level of expression of CASP8 protein to below that necessary for proper cellular regulation.”

The metes and bounds of “proper cellular regulation” cannot be determined and thus it is not clear what level of protein expression would meet this limitation. Specifically, it cannot be

Art Unit: 1642

determined what would be considered “proper cellular regulation” or how such regulation would be measured or determined, and thus it is not clear what would meet the limitations of the claims.

10. The previous grounds of rejection under 35 U.S.C. 102(e) as being anticipated by Hunter et al., US Patent 6,172,190, January 9, 2001 is applied to new/amended claims 2-3, 6-9, 13-14, 17-20, 27-29, 48-53, and 55.

US 6,172,190 teaches a method of diagnosis or prognosis of a cancer (a disorder associated with apoptotic cell death) by detecting inactivation of a CASP8 gene by detecting modification of CASP8 genomic DNA (which would include deletions). ‘190 teaches that these genomic mutations encompass mutations which result in alterations in Caspase-8 gene expression. ‘190 also teaches methods of detection of CASP8 inactivation by detecting the lack of a CASP8 protein using an immunoassay (western blot) or detecting a modification of DNA using a labeled nucleic acid probe, including oligonucleotide PCR primers which have at least 15 bases which specifically hybridize to CASP8, northern blot analysis, and the corresponding diagnostic kits (see for example column 5, lines 15-40, column 7, lines 52-column 8, line 4, column 9, lines 17-32, column 10, lines 16-40, column 13, line 56-column 14, line 9, column 18, lines 12-20, and column 21, line 16-column 22, line 7).

Applicant argues that the ‘190 patent fails to teach the absence of expression of at least one CASP8 allele, and does not discuss at all how CASP8 can be inactivated in cancer. Applicant further argues that the CASP-8i and CASP-8i variants disclosed in the ‘190 patent may

Art Unit: 1642

actually compete with other forms of CASP-8 and thus increased expression of these variants may result in decreased apoptosis. Applicant's arguments filed February 19, 2002 have been fully considered but they are not persuasive.

At column 7, lines 50-67, and at column 21, line 16-column 22, line 7, detection of increased or decreased expression of CASP-8 genes are discussed as they pertain to a condition associated with decreased expression of CASP-8, including a lack of expression. Applicant's argument that the '190 patent discloses variants whose over expression may result in increased apoptosis is not commensurate in scope with the claims, which merely determine measuring inactivation of the CASP-8 gene. As set forth above, CASP-8 inactivation, including CASP-8, and the CASP-8h or CASP-8i isoforms is associated with decreased apoptosis. Although the specification does disclose that some CASP-8h or CASP-8i mutations may increase apoptosis, it also clearly sets forth that inactivation of CASPASE-8, including CASP-8h or CASP-8i results in decreased apoptosis.

11. The previous grounds of rejection under 35 U.S.C. 103(a) as being unpatentable over Mandruzzato et al., J. Exp. Med., Vol. 186, No. 5, pages 785-793, August 29, 1997, (IDS), in view of Hunter et al., US Patent 6,172,190, January 9, 2001 or Dixit et al. WO 97/46662, published December 11, 1997 (IDS) is applied to new/amended claims 2-3, 6-9, 13-14, 17-20, 27-29, 48-53, and 55.

Art Unit: 1642

Mandruzzato et al. teaches a method of diagnosis or prognosis of a cancer (Head and Neck Cancer) by detecting inactivation of a CASP8 gene by detecting modification of CASP8 genomic DNA. (see abstract and page 789, last paragraph, bridging to page 790).

Mandruzzato et al. fails to teach detection of CASP8 gene modification including a lack of expression of a CASP8 allele, deletion, using nucleic acid primers, detection by immunoassay, or the corresponding kits.

US 6,172,190 teaches a method of diagnosis or prognosis of a cancer (a disorder associated with apoptotic cell death) by detecting inactivation of a CASP8 gene by detecting modification of CASP8 genomic DNA (which would include deletions). '190 teaches that these genomic mutations encompass mutations which result in alterations in Caspase-8 gene expression. '190 also teaches methods of detection of CASP8 inactivation by detecting the lack of a CASP8 protein using an immunoassay (western blot) or detecting a modification of DNA using a labeled nucleic acid probe, including oligonucleotide PCR primers which have at least 15 bases which specifically hybridize to CASP8, northern blot analysis, and the corresponding diagnostic kits (see for example column 5, lines 15-40, column 7, lines 52-column 8, line 4, column 9, lines 17-32, column 10, lines 16-40, column 13, line 56-column 14, line 9, column 18, lines 12-20, and column 21, line 16-column 22, line 7).

WO 97/46662 teaches methods of determining a gene mutation, including detecting a protein (or lack thereof) using immunoassay, and also detecting mutation using PCR and nucleic acid probe methods(see pages 45-55) .

Art Unit: 1642

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art to use the methods of determination of gene inactivation taught in US Patent 6,172,190 or WO 97/46662, to detect modifications of the CASP8 gene taught in Mandruzzato et al., and one would have been motivated to do so because other mutations of CASP-8 are likely and would be helpful in tumor studies, as taught in Mandruzzato et al. (see page 791).

Applicant argues that neither Mandruzzato et al., or the '190 patent disclose or suggest that inactivation of CASP8 gene in cancer results from the absence of expression of one or both CASP8 alleles. Applicant further argues that the '190 patent does not disclose or suggest use of oligonucleotide probes and PCR primers to detect gene inactivating mutations, and that WO 97/46662 does not teach CASP8, or the use of oligonucleotide probes and PCR primers to detect gene inactivating mutations. Applicant's arguments filed February 19, 2002 have been fully considered but they are not persuasive.

As set forth above, both Mandruzzato et al., and the '190 patent disclose that CASP-8 regulates apoptosis, and that aberrant CASP-8 expression can result in conditions characterized by a decrease in apoptosis, including cancer. Mandruzzato et al. discloses a method of diagnosis or prognosis of a cancer (Head and Neck Cancer) by detecting inactivation of a CASP8 gene by detecting modification of CASP8 genomic DNA, and that other CASP-8 gene mutations would be expected. (see abstract and page 789, last paragraph, bridging to page 790). The '190 patent, at column 7, lines 50-67, and at column 21, line 16-column 22, line 7, detection of increased or decreased expression of CASP-8 genes are discussed as they pertain to a condition associated

Art Unit: 1642

with decreased expression of CASP-8, including a lack of expression. The '190 patent does disclose use of oligonucleotide probes and PCR primers to detect gene inactivating mutations (see column 21, lines 39-61.) WO 97/46662 teaches ICE LAP-7, which interacts with FLICE, which is another name for CASP-8. Further WO 97/46662 is cited for it's general teachings regarding detection for diagnosis of a disease resulting from under expression of a protein due to a mutation, etc., described at pages 45-55, and representative of the general knowledge in the art.

12. The previous grounds of rejection under 35 U.S.C. 103(a) as being unpatentable over Mandruzzato et al., J. Exp. Med., Vol. 186, No. 5, pages 785-793, August 29, 1997, (IDS), in view of Hunter et al., US Patent 6,172,190, January 9, 2001, or Dixit et al. WO 97/46662, published December 11, 1997 (IDS), and further in view of Herman et al. (1), PNAS, Vol. 93, pages 9821-9826, September 1996, or Herman et al. (2), PNAS, Vol. 91, pages 9700-9704, October 1994 is applied to new/amended claims 2-9, 13-20, 27-29, and 48-57.

Mandruzzato et al. teaches a method of diagnosis or prognosis of a cancer (Head and Neck Cancer) by detecting inactivation of a CASP8 gene by detecting modification of CASP8 genomic DNA (see abstract and page 789, last paragraph, bridging to page 790).

Mandruzzato et al. fails to teach detection of CASP8 gene modification using nucleic acid primers, detection by immunoassay, or the corresponding kits, or detection of the specific CASP8 gene modification methylation of CASP8 promoter, using methylation polymerase chain reaction (PCR) assay.

Art Unit: 1642

US 6,172,190 teaches a method of diagnosis or prognosis of a cancer (a disorder associated with apoptotic cell death) by detecting inactivation of a CASP8 gene by detecting modification of CASP8 genomic DNA (which would include deletions). '190 teaches that these genomic mutations encompass mutations which result in alterations in Caspase-8 gene expression. '190 also teaches methods of detection of CASP8 inactivation by detecting the lack of a CASP8 protein using an immunoassay (western blot) or detecting a modification of DNA using a labeled nucleic acid probe, including oligonucleotide PCR primers which have at least 15 bases which specifically hybridize to CASP8, northern blot analysis, and the corresponding diagnostic kits (see for example column 5, lines 15-40, column 7, lines 52-column 8, line 4, column 9, lines 17-32, column 10, lines 16-40, column 13, line 56-column 14, line 9, column 18, lines 12-20, and column 21, line 16-column 22, line 7).

WO 97/46662 teaches methods of determining a gene mutation, including detecting a protein (or lack thereof) using immunoassay, and also detecting mutation using PCR and nucleic acid probe methods(see pages 45-55) .

Herman et al. (1) teaches that aberrant methylation, including promoter methylation is a common mutation in tumor suppressor genes in human cancers (see page 9821, first column). Herman et al. (1) also teaches the method of using methylation polymerase chain reaction (PCR) assay to detect promoter methylation mutations (see entire paper).

Art Unit: 1642

Herman et al. (2) teaches that aberrant methylation in regulator regions (which would include promoters) a common mutation in tumor suppressor genes in human cancers (see page 9700, first column).

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art to use the methods of determination of gene inactivation taught in US Patent 6,172,190, or to use the methods of detection of promoter methylation taught and discussed in Herman et al. (1) and (2) to detect modifications of the CASP8 gene taught in Mandruzzato et al., and one would have been motivated to do so because other mutations of CASP-8 are likely and would be helpful in tumor studies, as taught in Mandruzzato et al. (see page 791).

Applicant argues as set forth and rebutted above with regard to Mandruzzato et al., the '190 patent, and the WO 97/46662 patent. Applicant further argues that Mandruzzato et al. Teaches away from detecting mutations in non-coding regions by disclosing a mutation in a coding region. Applicant's arguments filed February 19, 2002 have been fully considered but they are not persuasive.

Applicants previous arguments were addressed in the previous rejections. With regard to the argument that the disclosure in Mandruzzato et al. Of a coding region mutation teaches away from a non-coding region mutation, this is not persuasive, because it is well known in the art that any number of different types of mutations can occur, and that the occurrence of one type of mutation does not preclude a different type, particularly in light of the teachings that other mutations are likely in both Mandruzzato et al. And Herman et al. (1) and (2) as set forth above.

Art Unit: 1642

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

Art Unit: 1642

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [\[anthony.caputa@uspto.gov\]](mailto:anthony.caputa@uspto.gov).

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

June 3, 2002


ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600